Cost Minimisation Analysis of Intravenous or Subcutaneous Trastuzumab Treatment in Patients with HER2-Positive Breast Cancer in Ireland

Gary L O'Brien[1], Cian O'Mahony[1], Katie Cooke[2], Ada Kinneally[3], Sarah-Jo Sinnot[4], Valerie Walshe[5], Mark Mulcahy[6], Stephen Byrne[1]

Mr. Gary L O'Brien, BPharm, MPharm

Mr. Cian O'Mahony, BPharm, MPharm

Ms. Katie Cooke, BPharm, BSc. Ther. Rad.

Ms. Ada Kinneally, BSc. Nursing, MSc.

Dr. Sarah-Jo Sinnot, BPharm, MPharm, PhD

Dr. Valerie Walshe, BA, MA, PhD

Dr. Mark Mulcahy, B.Comm, MSc, PhD

Professor Stephen Byrne, BSc. Pharmacy, PhD

[1]Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, College Road, Cork, Ireland

[2]Pharmacy Department, South Infirmary Victoria University Hospital, Cork, Ireland

[3]Oncology Department, University Hospital Waterford, Waterford, Ireland

[4]Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, WC1E7HT, UK.

[5]National Finance Division, Health Service Executive, Model Business Park, Model Farm Road, Cork, Ireland

[6]Department of Accounting, Finance and Information Systems, Cork University Business School, University College Cork, Cork, Ireland

Correspondence: Mr. Gary L O'Brien, BPharm, MPharm. Pharmaceutical Care Research Group, Cavanagh Pharmacy Building, University College Cork, College Road, Cork, Republic of Ireland. Tel: +353214901690. Fax: +353214901656. Email: gary_obrien@umail.ucc.ie

Correspondence: Professor Stephen Byrne, BSc. Pharmacy, PhD, Pharmaceutical Care Research Group, Cavanagh Pharmacy Building, University College Cork, College Road, Cork, Republic of Ireland. Tel: +353214901658. Fax: +353214901656. Email: stephen.byrne@ucc.ie

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Microabstract

This study analysed which route of trastuzumab administration, for the treatment of human epidermal growth factor receptor (HER)2-positive breast cancer, was more cost-effective and time saving in relation to active healthcare professional time. In clinical practice, trastuzumab subcutaneous treatment resulted in greater cost and time savings compared to trastuzumab intravenous treatment. At present, trastuzumab subcutaneous treatment should be considered a clinically equivalent and more cost-effective option to trastuzumab intravenous treatment.

Abstract

Background Two large acute Irish University teaching hospitals changed the manner in which they treated human epidermal growth factor receptor (HER)2-positive breast cancer patients by implementing the administration of trastuzumab via the subcutaneous (SC) route into their clinical practice. The study objective is to compare the trastuzumab SC and trastuzuamb intravenous (IV) treatment pathways in both hospitals and assess which route is more cost-effective and time saving in relation to active healthcare professional (HCP) time.

Materials and Methods A prospective observational study in the form of cost minimisation analysis constituted study design. Active HCP time for trastuzumab SC and IV-related tasks were recorded. Staff costs were calculated using fully loaded salary costs. Loss of productivity costs for patients were calculated using the human capital method.

Results On average, the total HCP time saved per trastuzumab SC treatment cycle relative to trastuzumab IV treatment cycle was 59.21 minutes. Time savings in favour of trastuzumab SC resulted from quicker drug reconstitution, no IV catheter installation/removal, and less HCP monitoring. Over a full treatment course of 17 cycles, average HCP time saved accumulates to 16.78 hours with an estimated direct cost saving of €1,609.99. Loss of productivity for patients receiving trastuzumab IV (2.15 days) was greater than that of trastuzumab SC (0.60 days) for a full treatment course.

Conclusion Trastuzumab SC treatment has proven to be a more cost-effective option than trastuzumab IV treatment that generated greater HCP time savings in both study sites. Healthcare policymakers should consider replacing trastuzumab IV with trastuzumab SC treatment in all eligible patients.

Introduction

Breast cancer is the most common cancer in women[1, 2]. The humanized monoclonal antibody trastuzumab is indicated for the treatment of both early and metastatic human epidermal growth factor receptor (HER)2-positive breast cancer [3]. In this group of patients, trastuzumab is administered every three weeks for one year (either 17 or 18 treatment cycles depending on the decision of the attending physician) in early breast cancer or, in the case of metastatic breast cancer until disease progression, by intravenous (IV) infusion at a dose calculated according to the patient's weight [3]. The duration of administration for trastuzumab IV in this condition is 90 minutes in the first administration (loading dose) and 30 minutes for consecutive treatment administrations (maintenance dose) [3]. In addition to the IV formulation, a subcutaneous (SC) formulation exists. It has an administration time of less than five minutes and is given by a single-use injection device (SID) or via handheld syringe (HHS). The dose is independent of the patient's weight. The SC formulation has demonstrated pharmacokinetics, efficacy, and a safety profile comparable to the IV formulation in patients with early HER2-positive breast cancer in the enHANced treatment with NeoAdjuvant Herceptin (HannaH) trial [4]. Both the safety and tolerability of Subcutaneous trastuzumab for the adjuvant treatment of Human epidermal growth factor receptor 2-positive early breast cancer (SafeHer) trial and the Preference for subcutaneous or intravenous administration of trastuzumab in patients with HER2-positive early breast cancer (PrefHer) trial have also corroborated these findings [5, 6].

There are two general approaches to costing healthcare: top-down and bottom-up. A top-down approach estimates the cost of an individual service on average, usually using routinely available data e.g. average per diem costs. Top-down costing studies tend to be relatively quick and straightforward to conduct, however they are also less precise and cannot provide information on individual factors driving the costs [7]. Disease-specific per diem costs (or daily cost) give the average daily cost for treatments in each disease category but may still be quite broad [7]. Case-mix groups yield the costs for each category of "case" or hospital patient and take length of stay into account. While this approach to costing is more precise than the aforementioned approaches, a bottom-up approach (micro-costing) generates a more precise estimate but is more onerous to perform. In micro-costing, all resources used are identified and then the unit costs of the resources are multiplied by the quantities used [7]. Studies examining the differences between the cost estimates produced by both top-down and bottom-up approaches have concluded that bottom-up approaches are preferable for estimating cost components which have a large impact on total costs (e.g. labour, expensive drugs), for services where there is wide variation in costs between patients, and for centres which are integrated within a larger hospital compared to independent centres [8-11].

Trastuzumab IV was first launched in Ireland in December 2000 while trastuzumab SC was launched December 2013 [12]. The release of trastuzumab SC came at an interesting time when Ireland began to restructure its healthcare funding system from one where hospitals are funded based on historical levels of funding adjusted for activity and patient mix to a prospective case based payment system (Activity Based Funding) [13]. This change is currently being implemented for in-patient and day-case activity and will subsequently include outpatient services [13]. Within the Activity Based Funding system, previously referred to as "Money Follows the Patient", prices will be set initially with reference to average prices, but with an overall aim to implementing best practice prices on an incremental basis [13]. Therefore, with respect to the contemporaneous reform in the Irish healthcare sector, the aim of this study was to estimate the total cost of providing trastuzumab treatments in two large acute Irish University teaching hospitals within the south/south west hospital group in the year 2018. The perspective of the Irish healthcare service provider was adopted, using a micro-costing approach, and the loss of productivity was calculated from a societal perspective. In the Irish context, this is the first economic evaluation examining the impact of switching trastuzumab formulations.

Materials and Methods

Hospital 1 – Nurse-led clinic

Hospital 1, a 431 inpatient and 85 day procedure beds teaching hospital, provides general medical, surgical and maternity care to approximately 0.5 million patients of southeast Ireland. This hospital is the designated cancer centre for southeast Ireland. In 2011, a group of patients in this hospital entered into the SafeHer trial [5]. In early 2014, this hospital began to switch patients from trastuzumab IV to trastuzumab SC and decided to introduce a dedicated trastuzumab SC clinic for patients with HER2-positive breast cancer. The approach of moving this cohort of patients out of the day oncology ward attempted to improve the patient journey. This hospital took the decision to resource the trastuzumab SC clinic with a dedicated clinical nurse specialist (CNS), rather than share the resources with the oncology day ward. Clinic times run from 09:30-16:00 where each patient receives an allocated 45-minute treatment slot with a 1:1 patient to nurse ratio.

Hospital 2 – Infusion clinic

Hospital 2 is a teaching hospital in the south of Ireland that has a designated bed complement of 192 beds and caters for up to 38,400 admissions and 72,500 outpatient attendances each year. In late 2015, the pharmacy department in this hospital made the decision to switch patients from trastuzumab IV to trastuzumab SC. Patients are given either a morning or afternoon appointment in the infusion clinic at this hospital where they are attended to on a first come, first served basis by a clinical nurse specialist as per entry into the patient log.

Cost Minimisation Analysis

We conducted a prospective observational study in a subgroup of healthcare professionals (HCP) and patients with HER2-positive breast cancer that attended both University hospitals between May and June 2018. All data were collected by GOB, COM, AK, KC. Both hospitals were each visited on four occasions between April and June 2018. Each observation consisted of measuring the time required to perform a specific task related to the preparation and administration of trastuzumab. To quantify active HCP time, the time actively invested in carrying out the tasks where differences between the routes of administration had been predicted, was observed. **Figure 1** shows the tasks that both trastuzumab SC and IV treatment pathways have in common where time estimates were recorded. Patients receiving adjuvant pertuzumab treatment were excluded. All observations were made using a stopwatch. Patient treatment room times (time between entrance and exit from treatment room), were inferred from active HCP times. Although not enough sample time estimates were recorded for each task to resemble a time and motion study, the estimates gathered were verified by the HCPs involved in the study as being a true reflection of average times spent on tasks in routine clinical practice. An average time for each task was subsequently calculated and used in the cost analysis. This methodology has been previously seen in the literature [14, 15]. When a sufficient amount of time estimates were recorded for a particular HCP activity associated with trastuzumab preparation, compounding and administration, a student's t-test was performed for the two groups. In all these instances, results were statistically significant (P values < 0.05). Overall, a micro-costing approach was adopted.

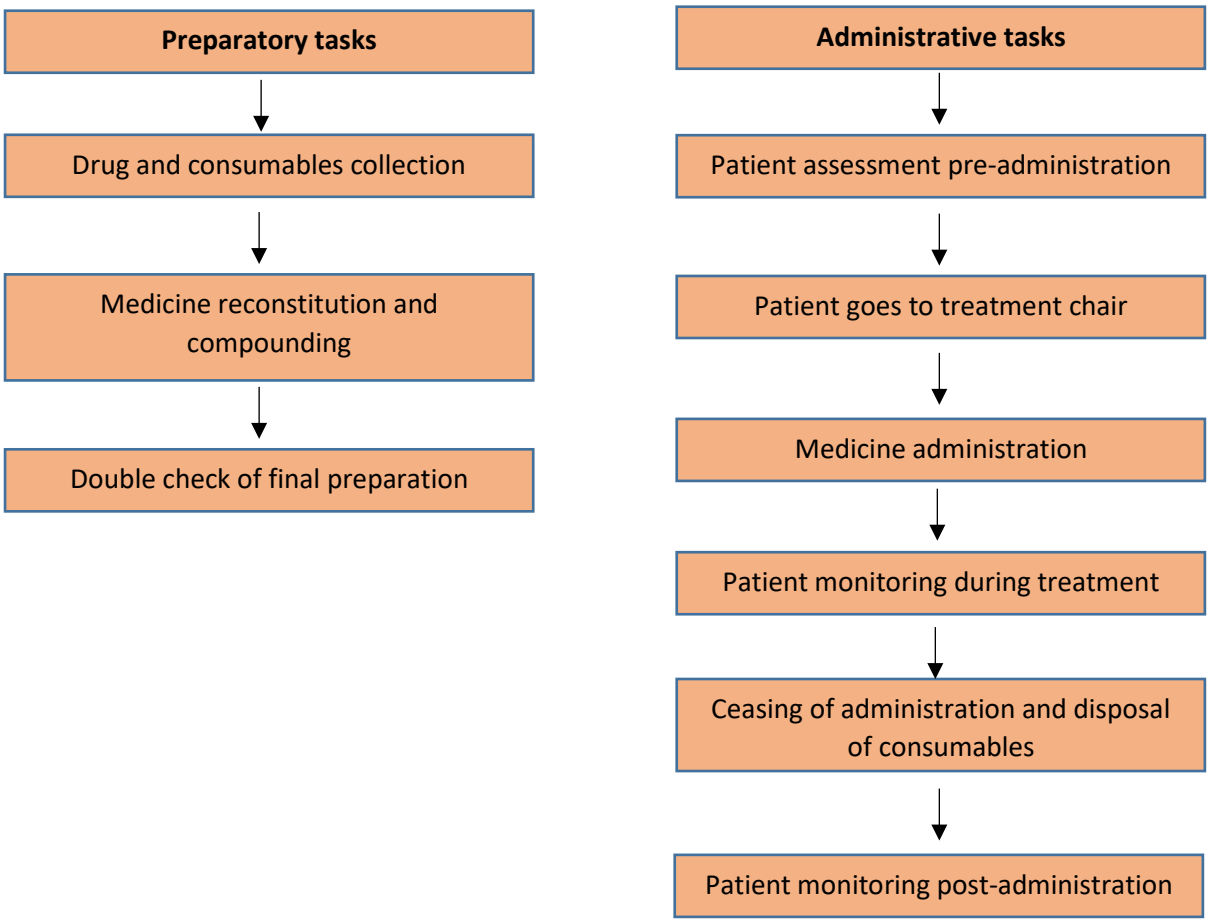
Direct and indirect costs were calculated. Direct costs included HCP costs for the tasks observed (nurses, pharmacists, and pharmacy technicians), costs of consumables, and drug costs. Indirect costs included the cost of lost productivity. Although both hospitals had been using trastuzumab SC since 2015, contemporaneously available healthcare costs, expressed in Euros (€) using 2018 prices (unless otherwise stated), were chosen. These updated costs provide a more accurate representation of current spending in the healthcare sector and are more useful in the preparation of a budget impact analysis, if required [16]. The perspective of the Irish public healthcare provider, the Health Service Executive (HSE), and the societal perspective were adopted. Evidence on resource use and patient health outcomes were collected by the research team during the course of the study and a retrospective review of patient medical records was conducted. However, this was of no major concern in this study given both trastuzumab formulations are clinically equivalent [4]. The time horizon for the study was less than 2 months thus discounting was not required. Multiple cost components were included in the analysis and are described. The mid-point of the HSE healthcare professional pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland [17, 18]. Salary was adjusted for employers' insurance cost, pension payments and general overheads (see **Table 1**). While the switching process in hospital 1 began in

2014 and in hospital 2 in 2015, the 2018 unit cost estimates were deemed appropriate for the analysis as medical inflation in Ireland was relatively stable during this period.

The costs of consumables were determined by retrieving invoices issued from the finance department from one of the large acute Irish University teaching hospitals in 2018 and calculating unit costs [19] (see **Table 2**). Drug costs were calculated according to the 2017 reported ex-factory prices (exclusive of value added tax (VAT)) of trastuzumab IV 150 mg (€567.69) and trastuzumab SC 600 mg (€1,645.24) [20]. The medicinal brand of trastuzumab used in both hospitals was Herceptin® and patients were administered the trastuzumab SC formulation via a SID [3]. All calculations were performed taking an average patient weight of 72.05 kg (average weight in Irish women aged 36–64 years [21]) treated with trastuzumab for 17 triweekly dosing cycles according to the data sheet guidelines where 17 cycles is considered one year of treatment/a full treatment cycle. Patient weights were retrieved from CliniChemo pharmacy management software. Patients' date of births (DOB) and sex were retrieved from i.PM (i.Patient Manager). In line with the standard clinical practice, all vials were considered used (vial sharing) in patients treated with trastuzumab IV resulting in no drug wastage. The effect of possible differences between reported and financed prices was assessed in a sensitivity analysis where discounts of 15% in the ex-factory price of the vial of trastuzumab IV and between 15 and 20% in the ex-factory price of trastuzumab SC were applied. These rates are believed to mimic national current commercially sensitive transactions offered by pharmaceutical manufacturers on biological medicines to Irish hospitals and are corroborated by the literature [22, 23]. The effect of differences in the weight of patients was analysed in another sensitivity analysis in which the costs of treatment in patients weighing between 65 and 75 kg were calculated. Vial sharing (no drug wastage) and dose banding tables from the National Cancer Control Programme (NCCP) [24] were used in association with the recommended triweekly maintenance dose of 6 mg/kg of body weight for trastuzumab IV [3].

Indirect costs were estimated using the human capital method [25] for inferred patient treatment room time. As applied in healthcare evaluation, the human capital approach has largely been used to value changes in the amount of time individuals are able to allocate to paid work as a result of illness or programmes to alleviate ill-health [26]. According to this approach, the gross wage becomes the unit of value for changes in paid working time resulting from healthcare programmes [26]. In the context of this study, where the healthcare programme, trastuzumab treatment, aims to reduce the patient's overall mortality risk, the change in productivity cost is represented by the present value of the stream of additional days in paid work over the duration of the patient's treatment cycle where each day valued using the gross wage. The average income liable for social insurance in Irish women aged 15-84 according to the Irish Department of Social Protection and Revenue Commissioners data, adjusted according to current (2018) consumer price index (CPI) inflation, (€27,206.40) [27, 28] was used in conjunction with the average recorded unemployment rate for Irish women aged 25–74 as of 2017 (5.4%) [29], and the average hours worked by women per week in paid employment in 2016 (31.7 hours) [30].

Figure 1 Common tasks conducted in the preparation and treatment of trastuzumab SC and IV



Guidelines and Ethical Considerations

This manuscript followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting health economic evaluations [31] (see Electronic Supplementary Material (**ESM) Table S1**). Ethical approval for this study was obtained from the clinical research ethics committee (institutional review board) of the local teaching hospitals network.

Table 1 Costs of healthcare workers

Job description	Gross annual salary(€)[(a)]	Total cost(€)/year[(b)]	Total cost(€)/min
Pharmacist	48,071	67,179	0.60
Pharmacy technician	38,447	53,730	0.48
Clinical nurse specialist	52,393	73,219	0.65
Staff nurse	37,508	52,417	0.47

(a) April 2018 Revised HSE Consolidated Pay scales [18].

(b) The mid-point of the HSE pay scale was used and adjusted according to guidelines for conducting economic evaluation in Ireland [17, 18].

Results

Direct costs

Costs of consumables

The cost of consumables per treatment cycle was €56.28 for trastuzumab IV and €25.91 for trastuzumab SC, a difference of €30.37 excluding the drug costs. For a complete 17-cycle treatment, the cost would be €956.76 for trastuzumab IV and €440.47 for trastuzumab SC, resulting in a saving of €516.29 per patient (see **Table 2**).

Table 2 Costs of consumables in patients treated with trastuzumab IV or trastuzumab SC during a treatment cycle

Different stages of a complete treatment cycle	**Cost of preparing 441mg dose (3x150mg vials) of trastuzumab IV(€) (72.05kg patient[(a),(b),(c)])**		**Cost of preparing a 600mg dose of trastuzumab SC[(c)] (€)**	
Equipment needed	**Number of items**	**Cost ex-VAT**	**Number of items**	**Cost ex-VAT**
Pre-cleaning of LAF				
70/30 IPA wipes	8	7.04	0	0
Preparation				
70% alcoholic wipes	20	1.40	14	0.98
70/30 IPA wipes	8	7.04	8	7.04
Sharps bin	1	1.35	1	1.35
Sterile surface mats	2	2.80	2	2.80
Chemo protect gowns	1	4.67	1	4.67
Face masks	1	0.68	1	0.68
Hand gloves	0	0	2	0.04
Elbow length sterile gloves	1	2.10	0	0
Head cap	1	0.02	1	0.02
Mini grip bags	1	0.08	1	0.08

Compounding				
Trastuzumab 150mg vials[(b)]	3	1669.01	0	0
Water for injection 10ml cartridges	3	0.27	0	0
10ml syringe	1	0.12	0	0
Pink needle	2	0.04	0	0
Seal for infusion bag	1	0.05	0	0
Sodium chloride 0.9% 250ml bag	1	0.79	0	0
30ml syringes	1	0.30	0	0
70/30 Sterile wipes	4	0.28	1	0.07
Clinichemo labels	2	0.04	2	0.04
Flag label	0	0	1	0.04
Green poly bags	1	0.06	1	0.06
Trastuzumab 600mg vial	0	0	1	1,645.24
5ml Syringe compatible with the closed system device	0	0	1	1.24
Vented vial access device/adapter 20mm	0	0	1	1.74
Cost of running LAF [(d)]	1	0.05	0	0
Administration				
Orange needle	0	0	1	0.02
Sodium chloride 10ml	0	0	1	0.07
Sterile swabs	0	0	1	0.06
Hand gloves	2	0.04	2	0.04
Fabric plasters	1	0.03	1	0.03
Alcoholic 2% chlorhexidine wipes	1	0.02	0	0
Rubber arm band	1	0.45	0	0
Cannula	1	0.70	0	0
Rubber bung for cannula	1	0.84	0	0
Securing tape	1	0.33	0	0
Opaque infusion giving set	1	5.83	0	0
Sodium chloride 50ml	2	1.30	0	0
Post-cleaning of LAF				
70/30 IPA wipes	8	7.04	0	0
Total Cost (ex-VAT):		1714.77		1,666.31
VAT on injectables and all consumables 23% VAT rate [32, 33]:		394.40		383.25
Total Cost (incl. VAT):		**2109.17**		**2049.56**

Key: IV – Intravenous, SC – Subcutaneous, VAT – Value Added Tax, LAF – Laminar air flow unit, IPA – Isopropyl alcohol

(a) The National Adult Nutrition Survey, which provides average weights, was used in the cost of compounding trastuzumab IV (Women: age 36-50 years = 70.5kg, age 51-64 years = 73.6kg, thus the mean weight for these prevalent age categories found with HER2-positive breast cancer is 72.05kg) [21].

(b) Dose banding information on trastuzumab IV provided by the NCCP for a 72.05kg patient required 441mg of drug (assume vial sharing/no drug wastage) at a maintenance dose of 6mg/kg [24] (initial loading dose was excluded). A 450mg dose is prepared in clinical practice to attain 441mg of drug.

(c) Cost of consumables were retrieved from invoices provided by the finance and resource department of the hospital 2 [19].

(d) Average cost of using a LAF for 900 seconds as per HCP trastuzumab reconstitution time where a conversion rate of 1 United States Dollar equals 0.86 Euros as of June 2018 is applied [34]. Trastuzumab IV was compounded by aseptic technique in the LAF. Trastuzumab SC was reconstituted safely on the bench using the closed system for immediate administration.

Healthcare professional costs

On average, the cost of HCP time invested in the preparation and administration of trastuzumab was €44.93 per cycle of trastuzumab IV and €9.83 per cycle of trastuzumab SC (see **Table 3 and Table 4**). For a complete 17-cycle treatment, this would result in a cost of €763.81 for trastuzumab IV and €167.11 for trastuzumab SC, with a cost differential of €596.70. Extrapolating these results to a hospital treating 25 patients per year with trastuzumab, as per hospitals in this study, the total HCP cost would be €19,095.25 if all patients received trastuzumab IV and €4,177.75 if all received trastuzumab SC, with an average saving of €14,917.50 (-78%) favourable to trastuzumab SC.

Table 3 Cost description associated with trastuzumab subcutaneous preparation, compounding and administration

Healthcare professional activity	**Recorded time estimate in Hospital 1 (secs)**	**Unit cost(€)**	**Recorded time estimate in Hospital 2 (secs)**	**Unit cost(€)**
Pre-check of prescription by pharmacist	55	0.55	53	0.53
Medicine preparation by pharmacy technician	[redacted]		54	0.43
Pharmacist double check of medicine			10	0.10

ID, blood pressure, temperature, pulse, blood tests, weight and ECHO check by CNS	342	3.71	331	3.59
Staff nurse double check of medicine	55	0.43		
Tray preparation for drug administration by CNS	15	0.16	10	0.11
CNS preparation (gloves and gowning)	108	1.17	113	1.22
Patient preparation (legs swabbed with alcohol wipe) by CNS	15	0.16	12	0.13
Medicine preparation by CNS	45	0.49		
Injection administration time by CNS	310	3.36	280	3.03
Patient after care (wipe and plaster) by CNS	20	0.22	25	0.27
Total	965 (16.08 minutes)	10.25	888 (14.80 minutes)	9.41
Average HCP time of both hospitals	**15.44 minutes**		**Average HCP cost of both hospitals**	**€9.83**
Key: CNS – Clinical nurse specialist, ID – Identification, ECHO – Echocardiogram, HCP – Healthcare professional				

Table 4 Cost description associated with trastuzumab intravenous preparation, compounding and administration

Healthcare professional activity	**Recorded time estimate in Hospital 1 (secs)**	**Unit cost(€)**	**Recorded time estimate in Hospital 2 (secs)**	**Unit cost(€)**
Pre-check of prescription by pharmacist	119	1.19		
Pre-check of prescription and tray materials by pharmacist			307	3.07
Preparation of medicine tray and alcohol wipe down of items by pharmacy technician	243	1.94	122	0.98
Compounding of medicine by pharmacy technician in LAF	998	7.98	882	7.06
Pharmacist double check of medicine	150	1.50	33	0.33
ID, blood pressure, temperature, pulse, blood tests, weight and ECHO check by CNS	351	3.80	372	4.03
Staff nurse double check of medicine	54	0.42	49	0.38
Tray preparation for drug administration by CNS	182	1.97	200	2.17
CNS preparation (gloves and gowning)	102	1.11	99	1.07

Patient preparation (cannulation) by CNS	401	4.34	345	3.74
Injection administration by CNS	1800	19.50	1800	19.50
Patient after care (wipe and plaster) by CNS	182	1.97	167	1.81
Total	4,582 (76.37 minutes)	45.72	4,376 (72.93 minutes)	44.14
Average HCP time of both hospitals	**74.65 minutes**		**Average HCP cost of both hospitals**	**€44.93**
Key: CNS – Clinical nurse specialist, LAF – Laminar air flow unit, ID – Identification, ECHO – Echocardiogram, HCP – Healthcare professional				

Drug costs

In the base case (reported ex-factory price inclusive of a VAT rate of 23% [32]) and a national average patient weight of 72.05 kg [21]), the total cost of a 17-cycle treatment would be €34,898.97 for trastuzumab IV and €34,401.97 for trastuzumab SC, resulting in a difference of €497.00. In the first sensitivity analysis (discount of 15% for trastuzumab IV and a range of discounts from 15% to 20% for trastuzumab SC), the cost differences between treatments ranged from €1,027.84 to €2,747.93 in favour of trastuzumab SC. In the subsequent sensitivity analysis (considering patient weights between 65 and 75 kg and where banded doses for trastuzumab IV, recommended by the NCCP, were applied [24]), the cost differences between treatments ranged from €-2,826.71 to €497.00. More extreme weights (i.e. patients ≥80 kg) could reach savings greater than €3,820.71.

Indirect costs

The average patient treatment room time of both study sites was 841 seconds for trastuzumab SC and 3,052 seconds for trastuzumab IV (assuming no waiting times for patients). Estimated indirect costs according to lost productivity inferred by patient treatment room time for a 17-cycle treatment per patient were €243.74 (loss of 2.15 working days) for trastuzumab IV and €67.15 (loss of 0.60 working days) for trastuzumab SC. Trastuzumab SC resulted in lower indirect costs per patient compared with trastuzumab IV.

Total costs

Direct costs were €36,619.54 for trastuzumab IV and €35,009.55 for trastuzumab SC, a net difference of €1,609.99 in favour of trastuzumab SC. When indirect costs were added, replacement of trastuzumab IV by trastuzumab SC for a full 17-cycle treatment would save €1,786.58 (see **Table 5**).

Table 5 Total costs in patients treated with trastuzumab IV or trastuzumab SC

Costs	IV(€)	SC(€)	Difference(€)
Direct costs	**36,619.54**	**35,009.55**	**1,609.99**
Healthcare professional costs	763.81	167.11	596.70
Consumable costs	956.76	440.47	516.29
Drug costs	34,898.97	34,401.97	497.00
Indirect costs	**243.74**	**67.15**	**176.59**
Total costs	**36,863.28**	**35,076.70**	**1,786.58**

Discussion

This study describes active HCP time invested in the preparation and administration of trastuzumab. A time saving of 79% is accrued by the replacement of trastuzumab IV with trastuzumab SC. In fact, the authors believe this is the highest recorded active HCP time saving where other studies report time savings of 51% in Spain, 48% in Canada and Russia, 36% in France, 31% in Denmark and 15% in Switzerland [35]. Greater available HCP time could result in improvements in the quality of care, with more time free for monitoring, other relevant medical duties or indeed providing patient information or comforting. In addition, by utilising trastuzumab SC in the place of trastuzumab IV, a saving of €596.70 per patient in active HCP time for a full 17-cycle treatment is gained. This result is consistent with those of international studies [36-39].

The reduction in patient treatment room time resulted in a difference in indirect costs of €176.59 per 17-cycle treatment in favour of trastuzumab SC, a conservative estimate that only considered lost productivity between entering and leaving the patient treatment room. Moreover, this reduction in patient treatment room time could allow the treatment of the same number of patients with fewer resources or more patients with the same resources. As well as the economic implications, quality of life may improve with the time savings associated with trastuzumab SC. Indeed, a key finding of the PrefHer study was that patients favoured trastuzumab SC as it accumulated more time saved for them relative to trastuzumab IV treatment [6]. Hence, more than just an estimate of costs from the social perspective, according to preferences conveyed, we see that the patient can be the main beneficiary. Quality of life is especially important to those patients with metastatic breast cancer as theirs is a chronic illness and so minimising the time spent in hospital is an important factor in survivorship.

Drug cost savings from switching to trastuzumab SC may be underestimated in this study. The National Adult Nutrition Survey was used in the cost of compounding trastuzumab IV, (Women: age 36-50 years = 70.5kg, age 51-64 years = 73.6kg, thus, the mean weight for these prevalent age categories found with HER2-positive breast cancer is 72.05kg). This average weight is an underestimate of the true patient weight as Ireland tackles a rising obesity problem [40]. The mean patient weight for between both centres was 73.44 kg with a range of 43.5kg-125kg. Therefore, by using the average recommended weight of 72.05kg, the trastuzumab IV formulation may appear less costly than it actually is in practice. As per sensitivity analyses, drug costs for trastuzumab IV are currently lower than drug costs for trastuzumab SC for patients only for patients weighing ≤ 69kg. For patients weighing ≥70 kg, drug costs for trastuzumab IV begin to drastically increase relative to drug costs for trastuzumab SC.

In addition, for the recommended weight of 72.05kg, a maintenance trastuzumab IV dose of 6mg/kg [3] would require 432.3mg of drug. This is rounded to 441mg according to the national dose banding tables [24] provided by the NCCP. This results in 9mg of drug remaining after each trastuzumab 150mg vial reconstitution. Over 17 triweekly cycles, this equates to 153mg of drug remaining. In this study, we assume vial sharing and no drug wastage. However, in clinical practice, it is unlikely this amount of drug would be utilised as 9mg of drug is a very small quantity to share at each treatment cycle juncture and vial sharing opportunities do not always arise

upon reconstitution. Therefore, it is possible that the cost of 17 triweekly cycles of the trastuzumab IV is appearing €712.22 cheaper per patient than it actually is. A loading dose of 8mg/kg is required for patients when starting trastuzumab IV therapy or if patients misses their scheduled dose of trastuzumab IV by more than one week [3]. This presents an additional cost for trastuzumab IV which was omitted in this analysis. There is no initial loading dose for starting treatment or missed treatment with trastuzumab SC [41] resulting in this formulation being a more cost-effective option under these circumstances.

The main limitation of the study was that not enough time estimates were recorded to conduct a time and motion analysis. Although the estimates gathered were verified by the involved HCPs as being a true reflection of average times spent on tasks in routine clinical practice, a time and motion study, which gathers data on HCP time required to complete the observed tasks, would reduce uncertainty surrounding such inputs. As per other time and motion studies investigating this trastuzumab formulation switch, it would have been desirable to record hospital time (time between entry and exit from the hospital), and patient travel to the hospital, or the time lost by accompanying persons, by means of patient interview when calculating indirect costs [22]. These measurements would capture a broader societal perspective. Two recent time and motion studies have demonstrated that a transition to both trastuzumab and rituximab SC formulations from their respective IV formulations resulted in saved patient chair and active HCP times [35, 42].

This study was carried out in only two centres where differences in clinical practice exist. At times, it was difficult to compare clinical practice procedures for the analysis. However, as this study was conducted in routine clinical practice settings yielding real world data, as opposed to a study within/alongside a randomised controlled trial, the results are more generalizable. This study's design and setting may also explain why the active HCP time savings value of 79% is numerically higher than those corresponding values reported by time and motion studies conducted within open-label randomised crossover studies [35]. Nonetheless, as trastuzumab SC gains traction in the Irish healthcare setting; further research in more hospital sites should be conducted to corroborate these study findings.

At the time of data collection, one of the 48 patients receiving trastuzumab treatment was male. However, as the epidemiology of women with HER-2 breast cancer is much greater in females than males [43], indirect costs and loss of productivity were calculated using statistics based on data gathered for Irish females. If this method was calculated for males, it is likely the indirect costs and loss of productivity would be greater based on data gathered for Irish males [27].

A potential limitation in this study is the issue of "dead time" i.e. the five minute time period required for trastuzumab IV to dissolve upon reconstitution [3] and its 30 minute infusion time. While it is potentially possible that the HCP could conduct other medical duties during this dead time, such tasks were impossible to cost. The issue of dead time and potential medical opportunity cost is a controversial one in the field of costing [44]. In addition, as best clinical practices are adopted in these two large Irish University teaching hospitals (e.g. vial sharing); it was observed that the CNS upheld their duty of care by monitoring patients closely during the 30 minute trastuzumab IV infusion period for fear of adverse drug reactions which limited their ability to perform other activities in parallel.

For trastuzumab IV, patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms [3]. For trastuzumab SC, patients should be observed for six hours after the first injection and for two hours after subsequent injections for signs or symptoms of administration-related reactions [41]. Follow-up time was excluded from the cost minimisation analysis, as no cost differential existed. In clinical practice, patients were strongly advised to remain in clinic for the recommended follow-up time but this was seldom adhered to by patients. This variability in follow-up time from patients was not measured which means the loss of productivity may be underestimated in this study. Paracetamol treatment (by mouth or by IV infusion) was recommended for both trastuzumab IV and SC treatment cycles. Therefore, as no cost differential exists, it too was excluded from the cost analysis. As with follow-up time, there was unpredictability in this variable too where some patients would take paracetamol and some patients would refuse.

At present, it can be argued that this study is only of interest to hospital budget decision-makers within the south/south west hospital group in Ireland. This issue also arose in a similar study where the results of an economic evaluation of propofol/fentanyl compared with midazolam/fentanyl on recovery in the intensive care unit following cardiac surgery was only of interest to the local hospital [45]. However, more Irish hospitals are beginning to use trastuzumab SC and following the successful implementation of trastuzumab SC in Europe, Oceania and South America [22, 46, 47], it is envisaged this formulation will penetrate the North American oncology landscape next. Furthermore, in relation to the current oncology field, biosimilar trastuzumab IV is now available [48]. It has been approved in Ireland since June 2018, where the biosimilar trastuzumab IV 150mg vial Herzuma® yields a drug cost of €401.86 (exclusive of VAT) [49]. This is in comparison to the Herceptin® IV 150 mg vial which yields a drug cost of €567.69 (exclusive of VAT) [20]. The individual summary of product characteristics for both medicinal products appear almost identical [3, 48] thus it can be assumed that medicine reconstitution and administration tasks are equivalent, meaning the only major differential between the two products is the drug acquisition cost. It is also worth noting that local commercially sensitive price reductions are sometimes offered to payers who switch to biosimilar medicines [50]. It will be interesting to see what impact biosimilar trastuzumab will have on the Irish and international markets.

Subcutaneous versions of different oncology therapies have been available for patients for a while now, however it is only recently that patient-relevant and hospital benefits are being assessed [35, 51]. Although open to debate, the literature seems to be favouring subcutaneous oncology treatments over intravenous oncology treatments in terms of patient preference, time and cost savings [6, 22, 35, 42, 46, 51, 52]. A recent International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Special Task Force report identified and defined a series of elements that warrant consideration in value assessments of medical technologies [53]. In the report, Lakdawalla *et al.* discuss that some medical technologies offer advantages over existing alternatives such as simpler dosing schedules, alternate routes of administration, or combination treatments. To the extent that these improve patient adherence to treatments and health outcomes, they may impact the estimation of the value of the medical technology in the aggregate [54]. It is evident from this study that the trastuzumab SC formulation offers this advantage over the trastuzumab IV formulation. Trastuzumab SC also reduces the need for cannulation of patients whose veins are often compromised due to previous therapies and tests.

In this study, we attempt to capture the societal perspective by calculating the loss of productivity via the human capital method as well as presenting the more common healthcare payer perspective. Sanders *et al*. recommended for the sake of consistency and comparability, analysts should report "reference cases" from two perspectives—the healthcare sector perspective and the societal perspective [55]. This was also corroborated by an ISPOR Special Task Force report [56]. In addition, Olsen and Richardson argue that the part of productivity effects may be included to the extent that it results in increased resources available for healthcare [57]. In fact, if the trastuzumab SC formulation was taken out of the secondary care setting and supplied to patients via their local pharmacy for self-injection at home, the loss of productivity would virtually be eliminated as patients could avoid going to hospital. In conjunction, this would alleviate some of the workload that the exhausted secondary care system already encounters. Ireland has devised a ten-year plan for health reform through political consensus called Sláintecare which is currently underway [58]. Its aim is to establish a universal, single-tier health service where patients are treated solely on the basis of health need but it also plans to re-orient the health system 'towards integrated primary and community care that is consistent with the highest quality of patient safety in as short a time-frame as possible [59]. In line with the overarching aim of Sláintecare, the transplantation of trastuzumab SC treatment to the primary care sector would also satisfy patient needs who prefer home and community based medical treatments [60].

Accurate cost data are essential for ensuring breast cancer services are effective, efficient, and equitable and costing information should be used to guide policy, planning and implementation in this field. This is particularly pertinent in the current situation in Ireland, as healthcare funding is undergoing restructuring [13]. As demands on the service increase due to greater numbers of patients [61] and more complex care, the cost data presented in this analysis will be available for cost-effectiveness evaluations of new drugs, technologies and models of care. This is the first study to evaluate the economic, financial and clinical impact of switching from

trastuzumab IV to trastuzumab SC in Ireland. The present study has implemented recommendations from the CHEERS statement to ensure that this manuscript presents a transparent high quality evaluation.

Conclusion

In conclusion, the replacement of trastuzumab IV by trastuzumab SC within two large acute Irish teaching hospitals has proven to be a more cost-effective approach reducing active HCP time, patient treatment room time, and therefore improving patients' quality of life. With respect to the Irish healthcare landscape, these reductions in time result in economic savings, more efficient resource use and improved quality of care. Trastuzumab SC reduces the cost of consumables. Dependent on the patient's weight and the hospital's policy on vial sharing, trastuzumab SC did not always result in drug cost savings. A full treatment cycle of trastuzumab SC results in total estimated direct cost savings of €1,609.99. Every year, between 400 and 500 new cases of HER2-positive breast cancer present in Ireland [61] where such patients would be potentially eligible for treatment with trastuzumab. The widespread use of trastuzumab SC for these patients would not only result in direct cost savings but would also lead to a reduction in indirect costs due to a decrease in the loss of productivity. These clinical and economic aspects demonstrate that trastuzumab SC results in benefits for patients, HCP, and indeed, wider society.

Clinical Practice Points

- In line with the current evidence, trastuzumab is the standard of care for HER2-positive breast cancer.
- The trastuzuamb SC formulation has demonstrated pharmacokinetics, efficacy, and a safety profile comparable to the IV formulation.
- There is an increasing body of literature that favours the use of trastuzumab SC over trastuzumab IV.
- In the Irish context, total HCP time saved per trastuzumab SC treatment cycle relative to trastuzumab IV treatment cycle was 59.21 minutes. Time savings in favour of trastuzumab SC resulted from quicker drug reconstitution, no IV catheter installation and removal, and less HCP monitoring.
- Average HCP time saved summed to 16.78 hours with a total estimated direct cost saving of €1,609.99. Loss of productivity for patients receiving trastuzumab IV (2.15 days) was greater than that of trastuzumab SC (0.60 days) for a full treatment course.
- Globally, active HCP time savings were similar to those reported in this study. Countries in Europe accumulated active HCP time savings as high as 51% whereas Canada cumulated time savings of 36%.
- When available, subcutaneous administration of trastuzumab is preferable in terms of cost effectiveness, patient convenience and satisfaction and should be recommended over intravenous administration of trastuzumab when possible.

Compliance with Ethical Standards

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Disclosure

The authors have no conflicts of interest to declare.

Ethical Approval

The research ethics committee (institutional review board) of the local teaching hospitals network approved the trial protocol.

Informed Consent

Written consent was not required.

Author Contributions

Gary O'Brien (GOB), Stephen Byrne (SB), Katie Cooke (KC), Ada Kinneally (AK) Sarah-Jo Sinnot (SJS), Valerie Walshe (VW), and Mark Mulcahy (MM) wrote the manuscript; GOB, KC and AK analysed the data; GOB, KC, Cian O'Mahony (COM) and AK retrieved study data.

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Journal of Economic Literature (JEL) Classification

This article is classified as I19 according to the JEL system.

Electronic Supplementary Material (ESM) Table S1

CHEERS checklist

Section/item	Item No	Recommendation	Reported Yes/No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Yes
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Yes

Section/item	Item No	Recommendation	Reported Yes/No
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Yes
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Yes
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	N/A
Measurement of effectiveness	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating costs and resources	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes
Currency, price date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A

Section/item	Item No	Recommendation	Reported Yes/No
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	N/A
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes
Characterising uncertainty	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Yes
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes

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